PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P077		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03317	05/11/1998	07/11/1997
International Patent Classification (IPC) or national classification and IPC A61K31/445		
Applicant ABERDEEN UNIVERSITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/06/1999	14.03.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Brück, M Telephone No. +49 89 2399 8735

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/03317

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-14 as originally filed

Claims, No.:

1-23 as originally filed

Drawings, No.:

1-6 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-23.

because:

☒ the said international application, or the said claims Nos. 1-23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	*
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

1. Claims 1-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. Subject matter

The independent claims relate to either the first medical use (claim 1), the second/further medical use (claim 18), or to a method of treatment (claim 21) of a topical formulation comprising, in essence, either a macrocyclic lactone antibiotic or an immunosuppressive macrolide and a permeation modulator for the treatment of a dermatological condition.
Further, they relate to the first medical use of a topical formulation comprising an immunosuppressive macrolide and a permeation modulator (claim 15).

2. Prior art

D1: DATABASE WPI Week 9631 Derwent Publications Ltd., London, GB; AN 96-306477 [31] XP002092952 & JP 08 133979 A (SANDO YAKUHIN KK,JP) 28 May 1996

D2: EP-A-0 474 126 (FUJISAWA) 11 March 1992

D3: EP-A-0 582 239 (RHONE-POULENC RORER) 9 February 1994

D4: EP-A-0 027 286 (PROCTER & GAMBLE) 22 April 1981

D5: WO 96 13249 A (SANDOZ) 9 May 1996

D6: DE 44 18 115 A (SANDOZ) 1 December 1994

D7: EP-A-0 273 202 (E. VAN SCOTT ET AL.) 6 July 1988

D8: EP-A-0 043 738 (PROCTER & GAMBLE) 13 January 1982

D9: EP-A-0 435 436 (PFIZER) 3 July 1991

3. Novelty

Independent claims 1, 15, 18, and 21 and dependent claims 7, 8, 9, 12, 13, 19, 20, 22, and 23 are not novel vis-à-vis D1, which has already disclosed a composition comprising either a macrocyclic lactone antibiotic or an immunosuppressive macrolide (cyclosporin/macrolide cpd.) and a permeation modulator (the permeation enhancer propylene glycol) for the treatment of a dermatological condition.

Independent claims 1, 15, 18, and 21 and dependent claims 2, 4-9, 13, 14, 16, 19, 20, 22 and 23 are not novel vis-à-vis D2, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (FK 506) and a permeation modulator (oleic acid) for the treatment of a dermatological condition (abstract, pages 5 and 6).

Independent claims 1, 18, and 21 and dependent claims 2, 3, 5, 6-8, 13, 14, 19, 20, and 22 are not novel vis-à-vis D3, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (Linolsäure) for the treatment of a dermatological condition (abstract, pages 3, 7, 8, 9 and 12).

Independent claims 1, 18, and 21 and dependent claims 2, 3, 7-9, 12,13, 19, 20, and 22 are not novel vis-à-vis D4, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (Linolsäure) for the treatment of a

dermatological condition (abstract, pages 8, 16 and 18).

Independent claims 1, 15, 18, and 21 and dependent claims 2, 4, 7-14, 16, 17, 19, 20, 22 and 23 are not novel vis-à-vis D5, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (FK506) and a permeation modulator (Propylene glycol) for the treatment of a dermatological condition (abstract, pages 5, 6, 9, 10 and 17).

Independent claims 1 and 15 and dependent claims 2, 4, 7, 8, 9, 16 and 17 are not novel vis-à-vis D6, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (sirolimus = rapamycin) and a permeation modulator (Propylene glycol) for the treatment of a dermatological condition (abstract, pages 7 and 9).

Independent claims 1, 18, and 21 and dependent claims 3, 7 and 20 are not novel vis-à-vis D7, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (hydroxyacids) for the treatment of a dermatological condition (pages 2 and 17).

Independent claims 1, 18, and 21 and dependent claims 2, 3, 5-12, 19, 20 and 22 are not novel vis-à-vis D8, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (alkenoic acids) for the treatment of a dermatological condition (pages 6, 11, 13, 16, and 32).

Independent claim 1 and dependent claims 3, 5, 6, and 7 are not novel vis-à-vis D9, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (alkenoic acids) for the treatment of various medical conditions (pages 3, 7 and claims 1 and 2).

4. For the assessment of the present claims 1-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can

also be dependent upon the formulation of the claims.
The EPO does not, for example, recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VII:

1. The requirements of Rule 5.1(ii) PCT are not met because documents D1-D9 are not identified in the description and the relevant background art is not briefly discussed.

Section VIII

1. Claims 1, 15, 18, and 21 refer to an amount which is characterized only by a result to be achieved--viz., "such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced"--which renders the claims unclear and is, therefore, not considered as defining (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 July 1999 (20.07.99)	
International application No. PCT/GB98/03317	**Applicant's or agent's file reference** P077
International filing date (day/month/year) 05 November 1998 (05.11.98)	**Priority date** (day/month/year) 07 November 1997 (07.11.97)
Applicant ORMEROD, Anthony, David et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   04 June 1999 (04.06.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

C. Carrié

Telephone No.: (41-22) 338.83.38

17

P[redacted]ENT COOPERATION TREA[redacted]

REC'D 16 MAR 2000

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P077		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03317	05/11/1998	07/11/1997
International Patent Classification (IPC) or national classification and IPC A61K31/445		
Applicant ABERDEEN UNIVERSITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

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   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
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   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/06/1999	14.03.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Brück, M Telephone No. +49 89 2399 8735

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/03317

I. Basis of th r port

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Claims, No.:

1-23 as originally filed

Drawings, No.:

1-6 as originally filed

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☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-23.

becaus :

☒ the said international application, or the said claims Nos. 1-23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
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Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	*
	No:	Claims	

2. Citations and explanations

see separate sheet

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The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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D9: EP-A-0 435 436 (PFIZER) 3 July 1991

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dermatological condition (abstract, pages 8, 16 and 18).

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Independent claims 1, 18, and 21 and dependent claims 3, 7 and 20 are not novel vis-à-vis D7, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (hydroxyacids) for the treatment of a dermatological condition (pages 2 and 17).

Independent claims 1, 18, and 21 and dependent claims 2, 3, 5-12, 19, 20 and 22 are not novel vis-à-vis D8, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (alkenoic acids) for the treatment of a dermatological condition (pages 6, 11, 13, 16, and 32).

Independent claim 1 and dependent claims 3, 5, 6, and 7 are not novel vis-à-vis D9, which has already disclosed a composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide (erythromycin) and a permeation modulator (alkenoic acids) for the treatment of various medical conditions (pages 3, 7 and claims 1 and 2).

4. For the assessment of the present claims 1-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can

also be dependent upon the formulation of the claims.
The EPO does not, for example, recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VII:

1. The requirements of Rule 5.1(ii) PCT are not met because documents D1-D9 are not identified in the description and the relevant background art is not briefly discussed.

Section VIII

1. Claims 1, 15, 18, and 21 refer to an amount which is characterized only by a result to be achieved--viz., "such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced"--which renders the claims unclear and is, therefore, not considered as defining (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P077		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/03317	05/11/1998	07/11/1997

Applicant

ABERDEEN UNIVERSITY et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 1
   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/445, 31/70, 38/13, 9/06, 47/12, 31/435

A1

(11) International Publication Number: WO 99/24036

(43) International Publication Date: 20 May 1999 (20.05.99)

(21) International Application Number: PCT/GB98/03317

(22) International Filing Date: 5 November 1998 (05.11.98)

(30) Priority Data:
9723669.9 7 November 1997 (07.11.97) GB

(71) Applicant *(for all designated States except US)*: ABERDEEN UNIVERSITY [GB/GB]; Auris Business Centre, 23 St. Machar Drive, Aberdeen AB2 1RY (GB).

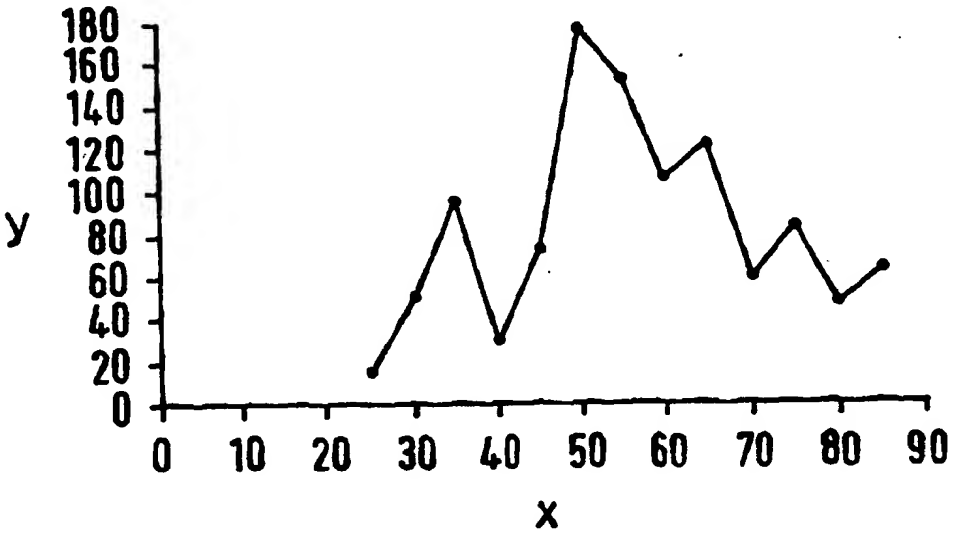
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ORMEROD, Anthony, David [GB/GB]; 12 Kemnay Place, Aberdeen AB15 8SG (GB). WINFIELD, Arthur [GB/GB]; 42 Westholme Avenue, Aberdeen AB15 6AB (GB).

(74) Agents: STEBBING, Peter, John, Hunter et al.; Ablett & Stebbing, Caparo House, 101–103 Baker Street, London W1M 1FD (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SKIN PENETRATION ENHANCING COMPONENTS



(57) Abstract

The present invention relates to a topical formulation for the treatment of a dermatological condition which comprises a macrocyclic lactone antibiotic, immunosuppressive macrolide or a biologically active analogue, derivative or pro–drug thereof; characterized in that it further comprises a permeation modulator and the permeation modulator and the macrocyclic lactone or macrolide or the biologically active analogue, derivative or pro–drug thereof are present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced. The immunosuppressive macrolide may be sirolimus.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

SKIN PENETRATION ENHANCING COMPONENTS

This present invention relates to an effective treatment for psoriasis and other dermatological conditions using a topically applied immunosuppressive agent. The preferred formulation does not allow the agent to appear in the blood or other circulatory system at any significant level.

Dermatological conditions can be uncomfortable and embarrassing for the patient, so an effective safe treatment is required. Some dermatological conditions are caused by an overactive immune system, examples are psoriasis, alopecia, lichen planus, lupus erythematosus, pyoderma gangrenosum, vitiligo and graft versus host disease. Others can be due to bacterial or pustular skin infections.

Dermatological conditions caused by an overactive immune system can be treated by immunosuppressive macrolides, for example sirolimus (rapamycin), FK-506 (tacrolimus) or SDZ ASM 981. Those that are caused by bacteria or are deeper skin infections, such as acne vulgaris and hidranitis suppcurativa, can be treated by macrolide antibiotics, for example erythromycin, azithromycin and clarithromycin. The above agents may be applied by means of topical creams and lotions or taken orally.

Psoriasis affects 2.4% of the population and the current understanding of the pathogenesis of the disease is that it is driven initially by immunocytes. These and keratinocytes are mutually stimulated and activated through the production of cytokines, TGFa, IL-6 and IL-8 from lymphocytes. This leads to a hyperproliferative epidermis with rapid 36 hour cycling of the transient amplifying compartment of

keratinocytes.

FK506 is a macrolide antibiotic which shows part homology with sirolimus. Research in models has shown that it has some efficacy in the topical therapy of contact dermatitis, atopic eczema and to a lesser degree psoriasis. Cyclosporin is also known to be effective in treating a wide range of skin diseases. However the usefulness of these drugs is limited by their potential side effects resulting from systemic administration.

Other forms of treatment of dermatological conditions may include using topical steroids but these have undesirable effects such as irreversible atrophy and purpura.

In the treatment of the human or animal body, one of the considerations is that any medicament shall as far as possible affect only the afflicted part. It is well known that amounts of circulating drug should be kept as low as possible to avoid unwanted mutations. A problem with the topical application of medicaments to the skin for example, is that the medicament tends to penetrate the skin and establish itself in the circulating blood system. This is not what is intended in the treatment of dermatological conditions.

The macrocyclic lactone antibiotic rapamycin for example as disclosed in EP-A-0533433 has already been used topically to treat such skin disorders as psoriasis and dermatitis. However no attempt has been made to reduce the amount of rapamycin translocated across the skin into the systemic system. Nor is there any discussion of the reduction of the levels of circulating rapamycin or other macrolide drug at the same time as providing therapeutically effective treatment for

a variety of skin disorders.

We have now found that this may be achieved by the addition to such drugs of a permeation modulator. Permeation enhancers are well known as a class of drug translocation facilitors, but the purpose of these is to increase the drug flux across the skin. A permeation modulator however has the facility to allow the drug to penetrate the skin, and particularly the stratum corneum, without significantly passing through the epidermis into systemic systems (eg the blood or lymph systems).

It is also known that immunosuppressive agents taken orally and steroids applied topically can be used to treat dermatological conditions, such as psoriasis or eczema. However, they are often non-specific in their action which leads to undesirable side effects. Thus it would be desirable to develop a topical delivery formulation for an immunosuppressive agent which preferentially treats the diseased sites only and avoids significant systemic exposure; so reducing harmful side effects.

Sirolimus is a macrocyclic lactone antibiotic produced by the organism *Streptomyces hygroscopicus;* it is known to have potent immunosuppressive activities. Sirolimus acts through specific binding of a family of cytosolic immunophilins called the FK binding proteins (FKBP). The sirolimus FKBP complex acts at least three sites. Firstly, by blocking the phosphorylation activation of p70 s6 kinase, an enzyme acting on the 40S ribosomal subunit s6 protein, thereby reducing the efficiency of translation. Secondly by preventing activation of specific elongation factors required for protein synthesis. Thirdly, it inhibits enzyme activity of the cyclin dependent

kinase cdK-cyclin E complex which forms one of the tight controls of the G1/S transition in cell division by inhibiting the normal decline of the p27 cdk inhibitor which would follow IL-2 stimulation. Sirolimus has an advantage over other immunosuppressive agents in the treatment of psoriasis as it has an inhibitory effect on keratinocyte proliferation. *In vitro* experiments have shown that this inhibitory effect takes place at concentrations ranging from 3-10μg/ml. A broader range may be employed for example 1 to 20μg/ml, but the more efficacious range is 5-8μg/ml.

According to the first aspect of the invention, there is provided a topical formulation for the treatment of a dermatological condition which comprises a macrocyclic lactone antibiotic or immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof; characterised in that it further comprises a permeation modulator and the permeation modulator and the macrocyclic lactone antibiotic, immunosuppressive macrolide or pharmacologically active analogue, derivative or pro-drug are present in relative amounts such that when a therapeutic amount is applied to the skin, a minimal systemic effect is produced.

By the term "minimal systemic effect", is meant that the amount of active principal detectable in the blood stream is preferably less than 0.3 ng/nl over 4 to 24 hours after administration, more preferably below 0.1 ng/ml over the same period.

Preferably the macrocyclic lactone antibiotic is selected from erythromycin, azithromycin or clarithromycin. These macrocyclic lactone antibiotics are effective for treating

pustular and bacterial skin infections such as acne vulgaris.

Conveniently the immunosuppressive macrolide is selected from sirolimus, FK-506 or SDZ ASM 981. Sirolimus is a favoured alternative because it is also an effective antibiotic which is useful in the microbiological preservation of the formulation. The microbiological properties of sirolimus are also helpful in the treatment of scalp and flexural psoriasis, seborrhoeic dermatitis and in secondarily atopic eczema.

In preferred embodiments the permeation modulator may be an alkanoic or alkenic acid, preferably having 6 to 20 carbon atoms such as capric acid, octanoic acid, oleic acid or acids or such acids of intermediate chain length. The permeation modulator aids the penetration of the immunosuppressive macrolide or macrocyclic antibiotic through the stratum corneum, the principle barrier to the penetration of drugs. The stratum corneum is an aggregate of the stacked, flattened skeletons of keratin filled cells interspersed with lipid monolayer structures and water. The addition of the permeation modulator to the formulation results in the partial disruption of the barrier components, particularly the lipid structures. A gradient of the drug can then be produced across the stratum corneum particularly, which facilitates the diffusion of the immunosuppressive macrolide or macrocyclic lactone antibiotic across the stratum corneum into the living epidermis. The relative concentrations of the macrolide or antibiotic and the permeation modulator are chosen so that only partial penetration of the skin occurs; the macrocyclic lactone antibiotics or immunosuppressive macrolides reach the areas which require treatment but significant absorption of the said drugs into the systemic circulation is avoided thus reducing the likelihood of any systemic side effects.

Conveniently the permeation modulator is used in conjunction with a solvent system which includes an aromatic alcohol such as phenyl-alkanol or a biologically acceptable benzene derivative, with or without an admixture of monoglycerides and/or a fatty acid ester (e.g. isopropyl myristate). Other solvents used, include benzaldehyde, benzyl benzoate and acetone. The combination of solvent and permeation modulator further optimises the passage of the immunosuppressive macrolide or the macrocyclic lactone antibiotic across the stratum corneum.

Preferably, the concentration of the macrocyclic lactone antibiotic or immunosuppressive macrolide is up to 10% by weight of the formulation. More preferably the concentration of the macrocyclic lactone antibiotic or immunosuppressive macrolide is either 0.5% to 5.9% or 6% to 12% by weight. Even more preferably the concentration of the macrocyclic antibiotic or immunosuppressive macrolide is either 1 to 5% or 6 to 8% by weight. A concentration of 0.05% to 2% is most preferable in the treatment of eczema. The term "% by weight" used herein refers to the "% by weight of the final formulation".

Preferably the above ranges of macrocyclic lactone antibiotic or immunosuppressive macrolide or analogue derivative or pro-drug thereof are used in an agent comprising a permeation modulator; wherein the concentration of the permeation modulator is 0.1% to 60% by weight. More preferably the concentration of the permeation modulator is either 0.1% to 39.9% or 40% to 80% by weight. Even more preferably the concentration of the permeation modulator is either 0.1% to 19.9%, 20% to 39.9% or 40% to 60%.

Preferably the above ranges of macrocyclic lactone antibiotic or immunosuppressive and permeation modulator are used in a formulation in conjunction with a solvent system; wherein the concentration of the solvent system is 5% to 90% by weight. More preferably the concentration of the solvent system is either 0.1% to 49.9% or 50% to 90% by weight. Even more preferably the concentration of the solvent system is either 0.1% to 19.9%, 20% to 39.9%, 40% to 69.9% or 70% to 90% by weight.

Preferably a thickening agent is present in the formulation. If the formulation is to be used topically, it should be of an appropriate consistency. Therefore, thickening agents such as cetostearyl alcohol or commercially available medical grade white soft paraffin may be added. These can reduce the penetration of the immunosuppressive agent but they are required for effective application. The formulations of the invention are particularly suitable for treatment of conditions of the scalp.

In addition to the liquid and solid vehicles set forth above, the formulations of the invention may additionally include one of the following:- flavouring agents, lubricants, solubilizers, suspending agents, filler and glidants.

The formulation can also be dissolved or suspended in any pharmaceutically acceptable liquid carrier or vehicle such as water or a pharmaceutically acceptable oil or fat. Such a liquid carrier or vehicle can contain other pharmaceutically acceptable additives such as solubilizers, emulsifier, buffers, preservatives, suspending agents, thickening agents, colouring agents, viscosity regulators, stabilizers or osmo-regulators.

The invention will now be described, by way of illustration only, with reference to the following examples, tables and figures accompanying the specification

Figure 1 is a graphical representation of the effect on the flux (μg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the capric acid and benzyl alcohol ratio, where x is the percentage of capric acid in the benzyl alcohol.

Figure 2 is a graphical representation of the effect on the flux (μg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the octanoic acid and benzyl alcohol ratio, where x is the percentage of octanoic acid in the benzyl alcohol.

Figure 3 is a graphical representation of the effect on the flux (μg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the oleic acid and benzyl alcohol ratio, where x is the percentage of oleic acid in the benzyl alcohol.

Figure 4 is a graphical representation of the effect on the flux (μg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the sirolimus concentration (mg/ml) (x) while keeping the capric acid to benzyl acid ratio constant.

Figure 5 is a graphical representation of the results of the clinical score (y) determined after application of the sirolimus formulation ( ) and the control (⁝⁝⁝) in Example 3.

Figure 6 is a graphical representation of the difference in the clinical score after application with sirolimus formulation in Example 3, where y is the number of subjects

in each group. A positive score (x) shows improvement with use of the active formulation.

Figures 1 to 4 were obtained by *in vitro* experimentation. The results were used to optimize the sirolimus concentration and the ratio of permeation enhancer and solvent used in *in vivo* experiments.

Example 1

A formulation was formed of 8% sirolimus and 92% of a vehicle of capric acid (50%) with benzyl alcohol (50%). This was tested in single application experiments on four individuals with normal skin. Venous blood samples were taken at 4, 7 and 24 hours after application and no significant levels of sirolimus were detected using MSGCMS, which is able to detect sirolimus levels down to 0.1ng/ml.

In parallel, skin biopsies were taken from the individuals after 7 hours, the biopsy samples were glued to a glass slide and serially sectioned horizontally into 4 layers each 0.7mm thick and extracted with acetonitrile. The results are given in Table 1.

Table 1 shows the tissue concentrations of sirolimus 7 hours after application of capric acid: benzyl alcohol (50:50) containing sirolimus at 8%. The horizontal skin sections were each 0.7mm. Accordingly, for example, the section of skin designated 2 was the horizontal layer of skin 0.7-1.4mm from the surface of the skin.

Section of skin 1=surface	Sirolimus concentration μg/mg			
	A	B	C	D
1	0.059	0.288	0.301	0.216
2	Not done	0.108	0.144	0.126
3	0.255	0.173	0.339	0.256
4	0.239	0.214	0.370	0.241

Example 2

A formulation of sirolimus (2.2%) in a vehicle comprising isopropyl myristate 40%, benzyl alcohol 10% and capric acid 50% was tested in single application experiments on three individuals with normal skin. Venous blood samples were taken at 4, 7 and 24 hours after application and no significant levels of sirolimus were detected using MSGCMS.

After 7 hours biopsy samples were taken from two of the individuals. These were bisected in parallel with the surface to give an upper and lower half, roughly corresponding to the epidermis and dermis. The skin was homogenised with acetonitrile and sirolimus concentration was determined by HPLC. The results are given in Table 2

Table 2 shows the tissue concentrations of sirolimus 7 hours after application of capric acid: isopropyl myristate: benzyl alcohol (50:40:10) containing sirolimus at 2.2%.

Level of skin segment	Sirolimus Concentration μg/mg	
	Subject A	Subject B
Upper (1)	0	1.5
Lower (2)	0.333	0.5

Example 3

A double blind, left-right comparison of the effect of applying topical sirolimus in formulations as described in Examples 1 and 2, to 24 patients with chronic (over three months) plaque psoriasis was conducted. (22 out of the 24 patients were eventually analysed.) A single target plaque was treated for the first 6 weeks with the lower potency formulation of Example 2. After this the active treatment was increased to the higher potency formulation of Example 1 for 6 weeks unless a clear improvement on one side had already occurred.

The study included adults with stable, clearly demarcated, chronic plaque psoriasis, and two, well matched, contralateral, comparable plaques about $50cm^2$ in area on opposite sides of the body. Subjects were all aged over 18 years, were able to apply creams and had no other significant medical problems. Transaminases were not more than twice the upper limit of normal and subjects were selected to avoid those likely to have a holiday in sunlight during the 6-12 weeks of the trial.

Before the trial started, there was a two week washout period in which only bland emollients were applied to the target lesions.

Treatment was randomised and double blind. Hands were thoroughly washed between the twice daily application of the test formulations. The active formulation was applied consistently to one plaque while a control comprising only the vehicle base was applied consistently to the plaque on the opposite side. Where possible the arms or elbows were selected as target areas as cross contamination is less likely at these

sites.

Assessments were done at weeks 0, 2, 4 and 6 on the low potency treatment and at 8,10 and 12 on the higher dose formulation, provided there were no signs or laboratory evidence of toxicity. Clinical scoring was done at each attendance and areas traced at the start and finish of treatment. Biopsies from active and control lesions were performed at the end of treatment or at withdrawal. Biopsies were not done if an adverse event such as a reaction to the application occurred as this would influence the measures being assessed.

The lesions were also assessed at fortnightly intervals with subjective scoring on a scale of 0-8 for erythema, thickening, and scaling. Objective measures of improvement were performed on both lesions at the end of each treatment period (low and high formulations). These included pulsed A scan ultrasound measurement of lesion thickness and erythema measured with a reflectance erythema metre, both were averaged over 5 areas in each psoriatic lesion and were validated using a previous study which was performed using betamethasome as a reference.

At each visit we measured the full blood count, biochemistry, including urea, electrolytes, liver enzymes, bilirubin, calcium, magnesium, uric acid, glucose, amylase, muscle enzymes, lipids and cholesterol. Sirolimus levels were performed every 2 weeks during therapy. Samples for sirolimus levels were stored at minus 80° C and shipped to a central reference laboratory for analysis by LC/MS/MS by Wyeth Ayerst Research.

In biopsies, epidermal thickness was measured and

immunoperoxidase immunohistochemistry done using the following antibodies to count cells in a blinded fashion:

Thus, antibody Ki-67 was used to give a measure of hyperproliferation in the epidermis and CD4 helper lymphocytes were used to give a measure of auto-immune activity which drives psoriasis.

Cell counting in tissues was automated, using computer assisted image analysis (Seescan). Data was analysed by Student's T test for paired data and Wilcoxon's test.

Comparison of the final scores, active vs placebo achieved significance at 0.032 by T test or Wilcoxon's test 0.0457, see Table 3 and Figures 5 and 6. The erythema measurements and ultrasound recordings were not significantly different. Three of the twenty-two patients developed contact sensitivity to the topical preparations one to benzyl alcohol, one to sirolimus and one to both of these.

The antibody tests with Ki-67 showed a significant reduction of proliferating cells from a mean of 83/mm^3 in control to 55/mm^3 with Sirolimus (rapamycin) to give a significance of P-0.027 (T test). Using CD4 cells control values were 61/mm^3 against 32.7/mm^3 means values following rapamycin to give a significance of P-0.0026 (T-test). The T-test were unpaired due to missing samples.

Table 3 shows the clinical response to topical sirolimus. The clinical score is measured on a scale of 0-24 with higher values indicating a better result, ultrasound thickness in mm and erythema measurement in arbitrary units.

	Sirolimus		Control		Significance
	Mean	S.D.	Mean	S.D.	
Clinical Score	11.2	5.8	9.1	4.8	p=0.032
Ultrasound thickness	2.99	0.6	2.96	0.72	NS
Erythema measurement	34.5	7.9	33.1	7.7	NS

These results show that penetration of sirolimus from a formulation described above does occur. It is thought that increased adsorption would occur through the scalp to effectively treat scalp psoriasis.

CLAIMS:

1. A topical formulation for the treatment of a dermatological condition which comprises a macrocyclic lactone antibiotic, immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof; characterized in that it further comprises a permeation modulator and the permeation modulator and the macrocyclic lactone antibiotic or macrolide or the pharmacologically active analogue, derivative or pro-drug thereof are present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

2. A formulation according to claim 1 comprising up to 10% by weight of the macrocyclic lactone antibiotic or the immunosuppressive macrolide or analogue, derivative or pro-drug thereof; the permeation modulator being present at 1 to 60% by weight.

3. A formulation according to either claim 1 or 2 wherein the macrocyclic lactone antibiotic is selected from erythromycin, azithromycin or clarithromycin.

4. A formulation according to either claim 1 or 2 wherein the immunosuppressive macrolide is selected from sirolimus, FK506 or SDZ ASM 981.

5. A formulation according to any preceding claim wherein the permeation modulator is an alkanoic acid or alkenic acid.

6. A formulation according to claim 5 wherein the alkanoic acid or alkenic acid is selected from capric acid, octanoic acid, oleic such acid or acids of intermediate chain length.

7. A formulation according to any preceding claim wherein the dermatological condition is selected from psoriasis, alopecia, eczema dermatitis, lichen planus, lupus erthematosus, pyoderma gangrenosum, vitiligo, graft versus host disease, pustular skin infections, bacterial skin infections or acne vulgaris.

8. A formulation according to claim 7 wherein the dermatological condition is eczema dermatitis and the concentration of macrocyclic lactone antibiotic or immunosuppressive macrolide is 0.05% to 2% by weight.

9. A formulation according to any preceding claim wherein the permeation modulator is used in conjunction with a solvent system.

10. A formulation according to claim 9 wherein the solvent system comprises an aromatic alcohol or a biologically acceptable benzene derivative, with or without an admixture of monoglycerides and/or a fatty acid ester.

11. A formulation according to either claim 9 or 10 wherein the permeation modulator comprises capric acid and the solvent system comprises benzyl alcohol.

12. A formulation according to any of claims 8 to 11 wherein the concentration of the solvent system is 5% to 90% by weight.

13. A formulation according to any preceding claim further comprising a thickening agent.

14. A formulation according to claim 13 wherein the

thickening agent is selected from white soft paraffin, cetostearyl alcohol, yellow soft paraffin, cetyl alcohol, steryl alcohol, divalent carboxylic acid soaps and carnauber wax.

15. A topical formulation for the treatment of a dermatological condition which comprises an immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof; characterized in that it further comprises a permeation modulator; and the permeation modulator and the macrolide or the pharmacologically active analogue, derivative or pro-drug thereof are present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

16. A formulation according to either claim 15 wherein the immunosuppressive macrolide is selected from sirolimus, FK506 or SDZ ASM 981.

17. A formulation according to claim 16 wherein the immunosuppressive macrolide is sirolimus.

18. The use in the manufacture of a topical composition for the treatment of a dermatological condition of a macrocyclic lactone antibiotic or an immunosuppressive macrolide or a pharmacologically acceptable analogue, derivative or pro-drug thereof characterised in that it further comprises a permeation modulator and the permeation modulator; the macrocyclic lactone antibiotic or the immunosuppressive macrolide or pharmacologically acceptable analogue, derivative or pro-drug thereof being present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

19. The use of claim 18 wherein the macrocyclic lactone antibiotic or immunosuppressive macrolide is present at up to 10% by weight of the composition.

20. The use of an immunosuppressant macrolide, a macrocyclic lactone antibiotic or a pharmacologically active analogue, derivative or pro-drug thereof in the preparation of a topical formulation as claimed in any one of claims 1 to 17.

21. A method for the treatment of a disease of the skin or muccosa which comprises applying thereto a topical composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide or a pharmacologically acceptable analogue, derivative or pro-drug thereof; characterised in that it further comprises a permeation modulator; and the permeation modulator, the macrocyclic lactone antibiotic or the immunosuppressive macrolide or pharmacologically acceptable analogue, derivative or pro-drug thereof is present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

22. A method according to claim 21 wherein the macrocyclic lactone antibiotic or immunosuppressive macrolide is present at up to 10% by weight of the composition.

23. A method according to claim 21 or 22 wherein the immunosuppressive macrolide is utilized.

Figure 1

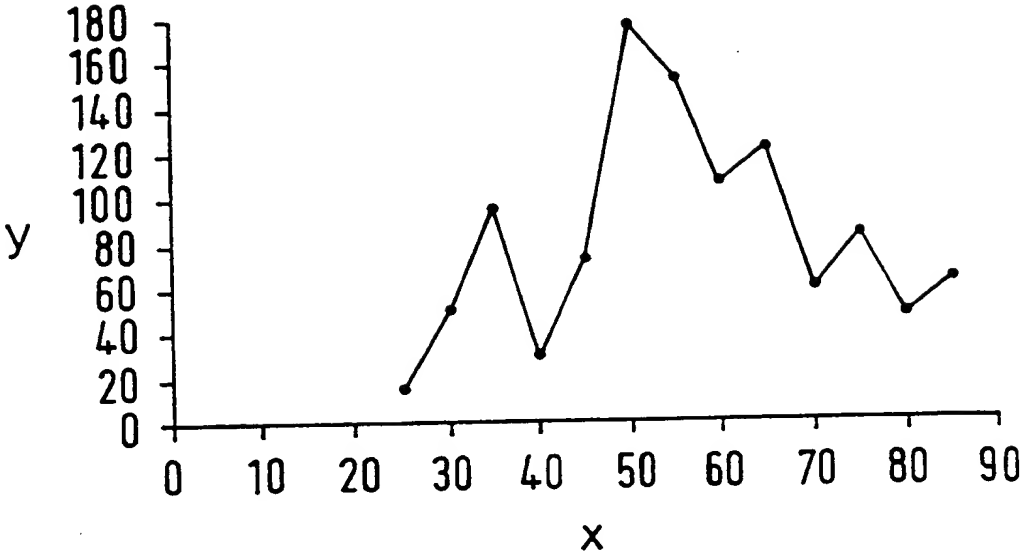


Figure 2

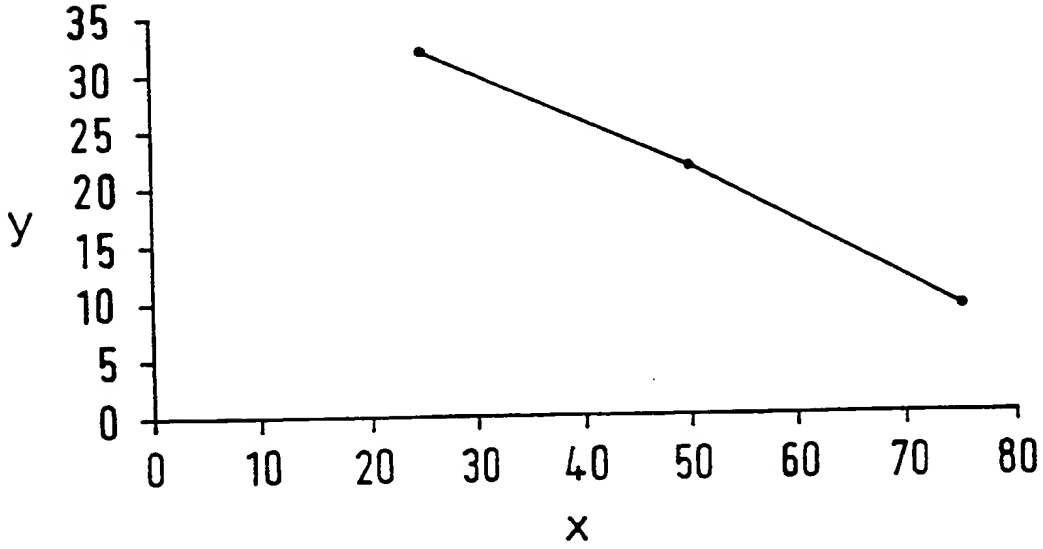


Figure 3

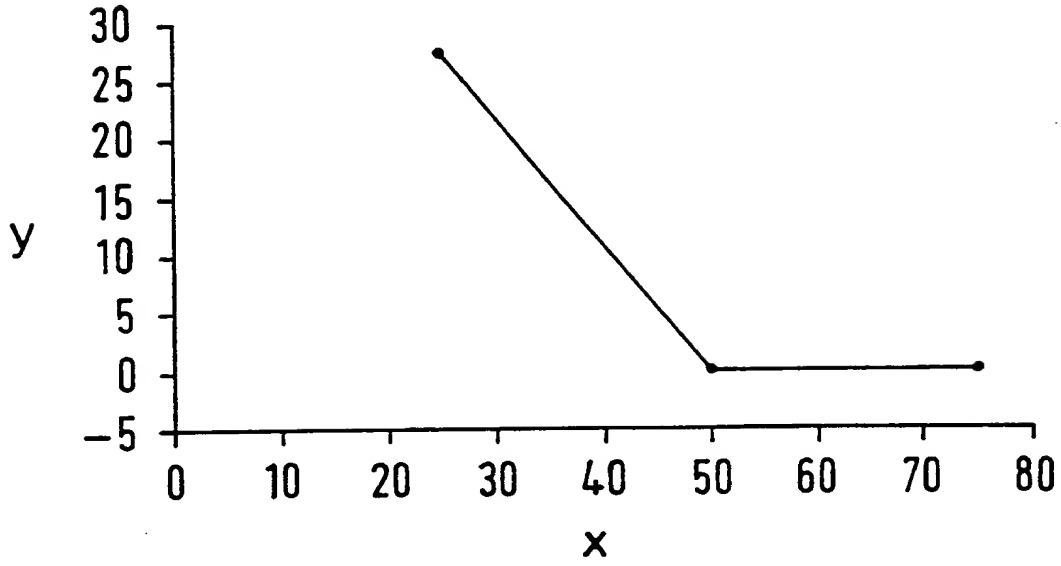


Figure 4

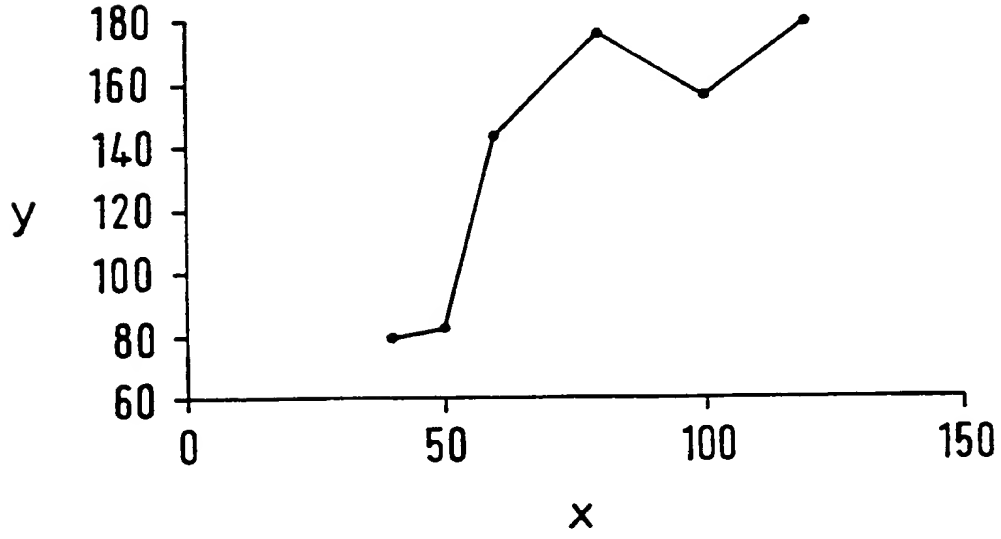


Figure 5

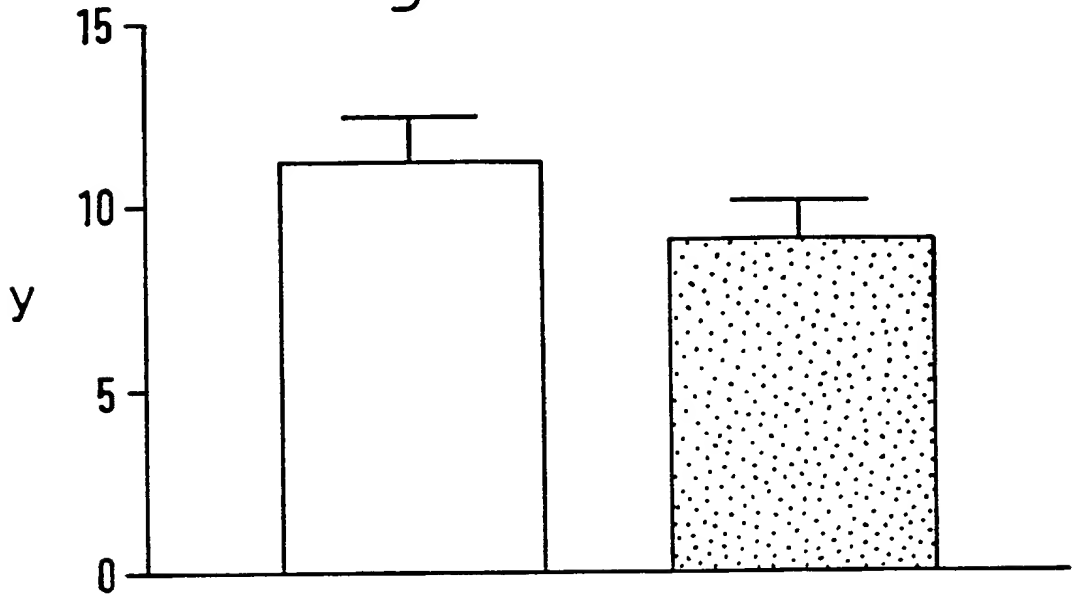
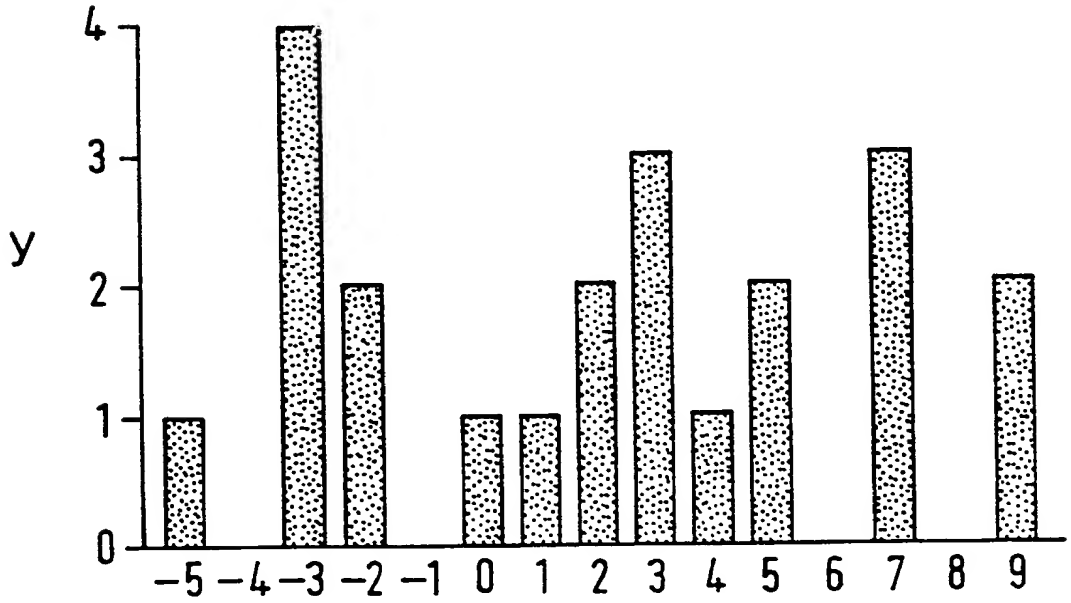


Figure 6



INTERNATIONAL SEARCH REPORT

Inter[redacted]pplication No
PCT/GB 98/03317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K31/70 A61K38/13 A61K9/06 A61K47/12
A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9631 Derwent Publications Ltd., London, GB; AN 96-306477 '31! XP002092952 ✓ see abstract & JP 08 133979 A (SANDO YAKUHIN KK,JP) 28 May 1996	1,2,13, 15,18-23
A	EP 0 474 126 A (FUJISAWA) 11 March 1992 see claims see page 5, line 24 - line 42	1-23
A	EP 0 582 239 A (RHONE-POULENC RORER) 9 February 1994 see claims see examples	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 1999	18/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte[illegible]pplication No
PCT/GB 98/03317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 335 115 A (E.D.THOMPSON ET AL.) 15 June 1982 see claims	1-23
A	EP 0 027 286 A (PROCTER & GAMBLE) 22 April 1981 see claims see table 1 see examples	1-23
A	EP 0 753 297 A (FUJISAWA) 15 January 1997 see claims	1-23
A	WO 96 13249 A (SANDOZ) 9 May 1996 see claims	1-23
A	DE 44 18 115 A (SANDOZ) 1 December 1994 see claims	1-23
A	EP 0 273 202 A (E. VAN SCOTT ET AL.) 6 July 1988 see claims	1-23
A	EP 0 043 738 A (PROCTER & GAMBLE) 13 January 1982 see claims see page 6, line 23 - line 25	1-23
A	EP 0 435 436 A (PFIZER) 3 July 1991 see claims 1-5,7	1-23

6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03317

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 21-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible] Application No
PCT/GB 98/03317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 474126 A	11-03-1992	AT 150304 T	15-04-1997
		AU 656145 B	27-01-1995
		AU 8351591 A	12-03-1992
		CA 2050623 A	05-03-1992
		CN 1059468 A	18-03-1992
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